Increased Physical Activity May Have a Positive Effect on Lipid Profiles in Pregnancy

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Abstract

During pregnancy, physiologic adaptations preserve maternal homeostasis while promoting fetal growth. Adaptations in the cardiovascular system and metabolic processes ensure adequate nutrients are available to the fetus while maintaining maternal homeostasis. For most women, these adaptations to pregnancy are tolerated uneventfully. In 2-8% of pregnancies, these maternal metabolic changes are not tolerated, resulting in more exaggerated increases in insulin resistance, LDL cholesterol, and triglycerides, as well as a reduction in HDL cholesterol (Roberts & Hubel, 2010). These metabolic abnormalities are present in the hypertensive pregnancy complication, preeclampsia. Preeclampsia shares risk factors and pathological features with cardiovascular disease. In both disorders, dyslipidemia and endothelial dysfunction are present and are associated with sedentary lifestyle and obesity. Some suggest that pregnancy is a cardiovascular stress test, and complications such as preeclampsia and gestational diabetes identify women who would benefit from preventative intervention to reduce cardiovascular disease. In the study "Exercise Intervention to Reduce Recurrent Preeclampsia" (RO1 NR05375), a group of women with a history of preeclampsia and a self-reported sedentary lifestyle were randomized into a walking group (n=62) and control group (n=61). Women were followed from the first trimester through delivery, and lipid profiles were assessed at 15.96±3, 24±2, and 36±2 weeks gestation. It was hypothesized that 30 minutes of physical activity, 5 days per week would minimize increases in glucose, triglycerides, and LDL and minimize decreases in HDL. Those in the walking group showed a significantly lower level of LDL (116.8±6.5 for walkers and 137.2±6.5 for controls, p=0.03) at 24±2 weeks gestation, but the intervention did not affect total or HDL cholesterol (p=0.10 and 0.68, respectively). This suggests that physical activity during pregnancy may minimize the increase in LDL or in other words, the "bad"

cholesterol. Future analysis of this data in relation to (1) the participant's adherence to physical activity, (2) body mass index, and (3) recurrent preeclampsia will enhance the understanding of these findings.

Background

Every minute, somewhere in the world a women dies as a result of pregnancy or childbirth ("Preeclampsia and Maternal Mortality", 2013). Preeclampsia and other hypertensive disorders account for 76,000 maternal deaths worldwide each year, and it is estimated these complications lead to the death of over 500,000 babies annually ("Preeclampsia and Maternal Mortality", 2013). If detected early, preeclampsia can be monitored and managed, and the chances of the progression to preeclampsia or other complex complications involving multiple system failures are greatly reduced. Due to lack of education, access to care, and inadequate health care services, the risk for maternal mortality is greatest for adolescent girls and women in developing countries ("Preeclampsia and Maternal Mortality", 2013). Proper prenatal care, good education, and an understanding of the cause behind preeclampsia are key in saving thousands of women's lives each year.

Preeclampsia first manifests itself after 20 weeks gestation in the second or third trimester of pregnancy ("Preeclampsia and Maternal Mortality", 2013). The primary symptoms of preeclampsia are (a) high blood pressure, (b) protein in the urine, (c) swelling, particularly in the face and hands, (d) headaches, and (e) changes in vision. These symptoms are oftentimes difficult to detect, and many women attribute these symptoms to "normal" signs of pregnancy ("Preeclampsia and Maternal Mortality", 2013). Hypertension is one of the greatest indicators of preeclampsia and is defined as blood pressure greater than 140/90 mmHg. Proteinuria is another key indicator as preeclampsia temporarily damages the kidney's ability to filter properly, and this causes protein to spill from the blood into the urine ("Preeclampsia and Maternal Mortality", 2013). Proteinuria is identified by 2+ protein on a dipstick or >300 milligrams in a 24 hour urine assessment (Spracklen et al., 2014). If these symptoms go undetected or unmanaged, the mother

is at a substantial risk for seizures (eclampsia), kidney failure, stroke, or death (Spracklen et al., 2014). The only known treatment for preeclampsia is premature delivery of the fetus which places the fetus at great risk for respiratory distress, intraventricular hemorrhaging, necrotizing enterocolitis, vision loss, and death ("Premature Babies", 2013).

While preeclampsia itself resolves with delivery, women with a history of preeclampsia face a considerable increase in the likelihood of developing cardiovascular disease ("Health Alert", 2016). Preeclampsia more than doubles the risk of a woman developing diabetes, cardiovascular disease, or suffering from a stroke later in life ("Health Alert", 2016). Some consider preeclampsia to be an early warning sign for the development of cardiovascular disease and therefore allows time for women to make the lifestyle changes necessary to prevent cardiovascular disease from occurring ("Health Alert", 2016). Research suggests that the primary mechanisms in preventing cardiovascular disease are (a) eating a heart-healthy diet, (b) not smoking, and (c) getting adequate physical activity each week. While these lifestyle changes are important in preventing cardiovascular disease later in life, some believe adequate diet and exercise may be the keys in preventing the development of preeclampsia as well ("Health Alert", 2016).

Review of the Literature

Since the late 1980s, researchers have suspected that endothelial damage is a key process in the development of preeclampsia. Subsequent research has found that in preeclampsia, there is a reduction in placental perfusion that results in an abnormal inflammatory response (Roberts, Hubel, 2009). This inflammation causes a significant increase in circulating free radicals which damage cells and cause widespread endothelial cell damage and dysfunction (Roberts, Hubel, 2009). This widespread endothelial damage affects the ability of the endothelium to regulate blood pressure and is further accentuated by the significant dyslipidemia that is also present in preeclampsia (Roberts, Hubel, 2009). Endothelial dysfunction and dyslipidemia are the two most prominent mechanisms that lead to the development of this complex disorder and therefore are the primary targets for preeclampsia research.

Because triglycerides and cholesterol are involved in the development of endothelial dysfunction, these lipids were assessed in normal pregnancy and in pregnancies complicated by preeclampsia. There has been significant and consistent evidence that demonstrates lipid levels, specifically triglycerides and cholesterol, between normotensive and preeclamptic women are quite different throughout the three trimesters of pregnancy (Diareme, Karkalousos, Theodoropoulos, Strouzas, & Lazanas, 2009). In normal pregnancy, there are marked changes in the sex hormones of estrogen and progesterone, which lead to substantial changes in lipid levels as well (Diareme et al., 2009). This change is known as physiological dyslipidemia, and these changes in lipid levels are best seen in total cholesterol and triglyceride levels (Diareme et al., 2009).

During the first trimester, the body needs an increased storage of energy to fulfill maternal and fetal metabolic needs. In order to compensate for these changes, there is an increase

in body fat storage and lipogenesis occurs, resulting in higher triglyceride levels early in pregnancy (Knopp et al., 1986). During late pregnancy, hypertriglyceridemia occurs as a means of developing milk formation right before delivery. This is seen as the triglyceride levels undergo a 2-3 fold increase during the third trimester of pregnancy (Knopp et al.,1986).

Maternal cholesterol is important to the fetus during early gestation as it promotes the accumulation of fat storage and serves as calories for the mother and the fetus during the first two trimesters of pregnancy (Knopp et al., 1986). Subfractions of cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) cholesterol levels peak midgestation at a 1.45 fold increase and subsequently decline to 1.15 fold at term as its importance during late pregnancy becomes increasingly minimal as the fetus' ability to synthesis cholesterol on its own begins to develop (Diareme et al., 2009). Low-density lipoprotein (LDL) cholesterol on the other hand, increases 2.5 fold throughout the pregnancy and reaches its peak at term (Knopp et al., 1986).

Women who develop preeclampsia have significantly higher triglyceride and cholesterol levels as early as the second trimester; thus early pregnancy lipid measure may be beneficial in determining who is at higher risk for developing preeclampsia during her pregnancy (Spracklen et al., 2014). Although it is still unclear whether hypertriglyceridemia is indicative of preeclampsia, studies have shown that elevated triglyceride levels are strongly correlated with the presence and severity of proteinuria, indicating that these lipid levels may be associated with the endothelial damage present in preeclamptic women (Lima, Andrade, Ruschi, & Sass, 2011). While the results are not fully consistent, numerous other studies have found that maternal serum total cholesterol and LDL levels significantly increase during the first, second, and third trimesters of preeclamptic pregnancies and that these levels change at a greater rate throughout

each trimester (Spracklen et al., 2014). In contrast, HDL levels were found to be significantly lower in preeclamptic women when compared with normotensive women (Spracklen et al., 2014).

Another major contributor to the development of preeclampsia is maternal endothelial dysfunction due to an imbalance between placental factors and maternal adaptation to these factors. During pregnancy, the placenta allows for the exchange of nutrients, oxygen, and waste between the mother and fetus (Sanchez-Aranguren, Prada, Riano-Medina, & Lopez, 2014). After the first trimester, the placenta undergoes a process of remodeling in which the maternal arteries supplying the placenta change from low capacity to high capacity (Sanchez-Aranguren et al., 2014). While in most pregnancies this change occurs without complication, in preeclampsia there is an incomplete tolerance to the trophoblasts released, and the remodeling of the vessels is reduced. This leads to a reduction in placental oxygenation, and in order to compensate for the lack of blood flow, the mother develops hypertension (Sanchez-Aranguren et al., 2014). The placenta then releases a number of inflammatory factors that lead to a systemic vascular response with endothelial dysfunction (Spracklen et al., 2014). This endothelial dysfunction is characterized by vasoconstriction and excessive clotting and is found in both preeclampsia and cardiovascular disease (Roberts, Taylor, Musci, Rodgers, Hubel, & McLaughlin, 1989).

Women with a history of preeclampsia have more than twice the risk of dying from early onset cardiovascular disease than women with a history of normal pregnancies (Powe, Levine, & Karumanchi, 2011). While the mechanisms that account for the correlation between preeclampsia and the development of cardiovascular disease later in life are not fully understood, the shared endothelial dysfunction present in both diseases may be a contributor. In addition to endothelial dysfunction, it has been demonstrated that elevated cholesterol and triglyceride levels

are directly associated with the development of cardiovascular disease (Goldberg & Elliot, 2015).

Finally, there is a significant correlation between the predictive risk factors for cardiovascular disease and preeclampsia including (a) insulin resistance, (b) maternal age >40, (c) obesity, (d) diabetes mellitus, and (e) renal disease (Powe, et al., 2011). Because of this, it is possible that the shared risk factors may jointly predispose women to preeclampsia, endothelial dysfunction, and cardiovascular disease, and the steps taken to prevent cardiovascular disease in women may also work to prevent preeclampsia as well.

Exercise is one of the most commonly used interventions in the prevention of cardiovascular disease, as exercise has been shown to positively affect lipid metabolism in individuals by decreasing triglyceride levels and increasing HDL cholesterol levels in certain individuals (Goldberg & Elliot, 2015). However, according to the Center for Disease Control (CDC), only one in five American adults meet the recommended exercise requirements of 150 minutes of moderate intensity aerobic activity each week (National Center for Health Statistics, 2013), and pregnant women have been found to exercise even less frequently (Fell, Joseph, Armson, & Dodd, 2009).

Having examined the effects of exercise on lipid metabolism, a study was created to test whether exercise during pregnancy would reduce the recurrence of preeclampsia in a group of sedentary women with a history of a preeclampsia. In this study, participants were randomized into a walking group or control group. Women who were placed in the walking group were instructed to walk at a moderate pace for 30 minutes, five days a week. All participants received telephone calls from a project nurse every two weeks and three face-to-face visits. During those visits, women in the walking intervention received instructions and support relative to walking

with an emphasis on problem-solving any barriers that would arise. Women in the control group received attention-control interactions. During these sessions, the women were provided with general health and pregnancy information. The primary aim of the study was to examine the effect of exercise on the recurrent development of preeclampsia. One of the secondary aims was to explore the effect of exercise on lipid metabolism in the women as it relates to the development of preeclampsia. The focus of this study is this secondary aim. Using the data, the research question for this study was: How does exercise affect the pattern of lipid metabolism during pregnancy for women who have a history of preeclampsia in a previous pregnancy and therefore an elevated risk of recurrent preeclampsia?

Purpose of the Study

The purpose of this study was to examine the effects of a moderate-intensity exercise intervention on triglyceride, cholesterol, HDL, LDL, insulin, and glucose levels at three points throughout pregnancy, specifically noting any significant differences in the metabolic changes of those in the intervention and control group at baseline, time 2, or time 3. We hypothesized that 30 minutes of moderate intensity physical activity performed five days per week would minimize increases in serum triglycerides, LDL cholesterol, glucose and insulin, as well as minimize decreases in HDL cholesterol in previously sedentary women with a history of preeclampsia.

Methods

This descriptive study used data collected in a randomized controlled study entitled *Exercise Intervention to Reduce Recurrent Preeclampsia* (R01NR05275). In that study, a group of pregnant women with a history of preeclampsia were randomized to a walking intervention group or an attention control group to determine if increasing exercise during pregnancy could reduce the rate of reoccurring preeclampsia. Behavioral and clinical data were obtained at three points throughout pregnancy and analyzed to compare the metabolic changes that the women in the control and intervention group underwent throughout their pregnancy.

Sample

Participants of the original study were recruited from an urban hospital in the Northeastern United States. All participants were pregnant, had a history of preeclampsia with the same partner, and self-reported a sedentary lifestyle. Individuals were excluded from the study if there was found to be an existing medical condition present that increased the risk for developing preeclampsia such as hypertension, diabetes, multiple gestation, or if the woman had a history of more than one prior preeclamptic pregnancy as this would increase the likelihood of recurring preeclampsia and act as a confounding factors to the study's results.

Instrument

Laboratory analyses were conducted at the Heinz Laboratory at the University of Pittsburgh Graduate School of Public Health. Heinz Laboratory has the required levels of proficiency to be included in the CDC-NHLBI Lipid Standardization Program. The analyses of glucose, triglycerides, and cholesterol were accomplished using enzymatic procedures, and insulin was analyzed using a radioimmunoassay procedure. For each of these procedures, duplicate samples with standards, control sera, and serum calibrators were included in each run.

The coefficient of variation was calculated between runs, and intra- and inter-assay coefficients of variation were calculated. The resulting coefficients were within an acceptable range. LDL cholesterol is often calculated indirectly using the Friedewald (1972) equation: LDLc = Total Cholesterol - HDLc - 0.2 (total TG). This calculation is not applicable if total triglycerides > 400 mg/dl. A substantial number of women who develop preeclampsia will evidence triglyceride concentration in excess of 400 mg/dl. For these subjects, LDL will be directly measured. These results will be used to compare metabolic differences in exercising and non-exercising pregnant women at 15.96±3, 24±2, and 36±2 weeks gestation.

Procedure

During the course of the randomized trial, participants had a fasting blood sample drawn at 15.96±3, 24±2, and 36±2 weeks gestation during a visit to the clinical research lab at Magee Women's Hospital.

Data Analysis

Results of the laboratory analyses were entered into a relational database and exported to the Statistical Program for the Social Sciences (SPSS). Descriptive and inferential statistics were used to describe the sample and lipid changes throughout pregnancy and to test for differences in lipid values between the intervention and control group

Results

Sample

One hundred twenty three pregnant women were enrolled in the study. The participants were randomized into a walking intervention group (p=62) and a control group (p=61). Participants entered the study at an average gestational age of 15.96 ± 3.02 weeks (mean ± SD)

and had a racial distribution of 79.7% Caucasian and 19.5% African-American. The participants ranged in age from 28.6 ± 5.25 years. There were no significant differences in demographics for the two study groups

Table 1

Demographic Data of study participants at entry to the study

	Walking Intervention Group	Control Group
Number of Women	62	61
Age at enrollment (mean ± S.D.)	28.47 ± 5.26	28.79 ± 5.29
Gestational age in weeks at enrollment (mean ± S.D.)	16 ± 3.20	15.87 ± 2.86
Race	33 W/ 9 B	46 W/ 15 B

Participant retention was a considerable challenge faced during the study. The participants' history of preeclampsia placed them at high-risk for reoccurrence (20%). Because of this, during scheduled gynecology check-ups, any subjective or objective data that varied from the expected baseline oftentimes resulted in doctors suggesting that the woman stop exercising. As a consequence, only 80 women completed the three blood draws at all three points, resulting in a total dropout of 34.9%. At the end of the study, the walking group had a sample size of 37 women, and the control group had a sample size of 43 women.

Lipid Metabolism

Participants' triglyceride, total cholesterol, LDL, HDL, insulin, and glucose levels were obtained and analyzed at 15.96±3, 24±2, and 36±2 weeks gestation. The lipid levels collected at each time point were analyzed as walking intervention group or control group. The mean lipid level at each time point was calculated and charted as a line graph. Standard error was calculated at each point to compare the sample's lipid levels results to that expected from the population. Finally, a T- test was run for each lipid in order to determine if there was a significant difference between the walking and control group at any time point.

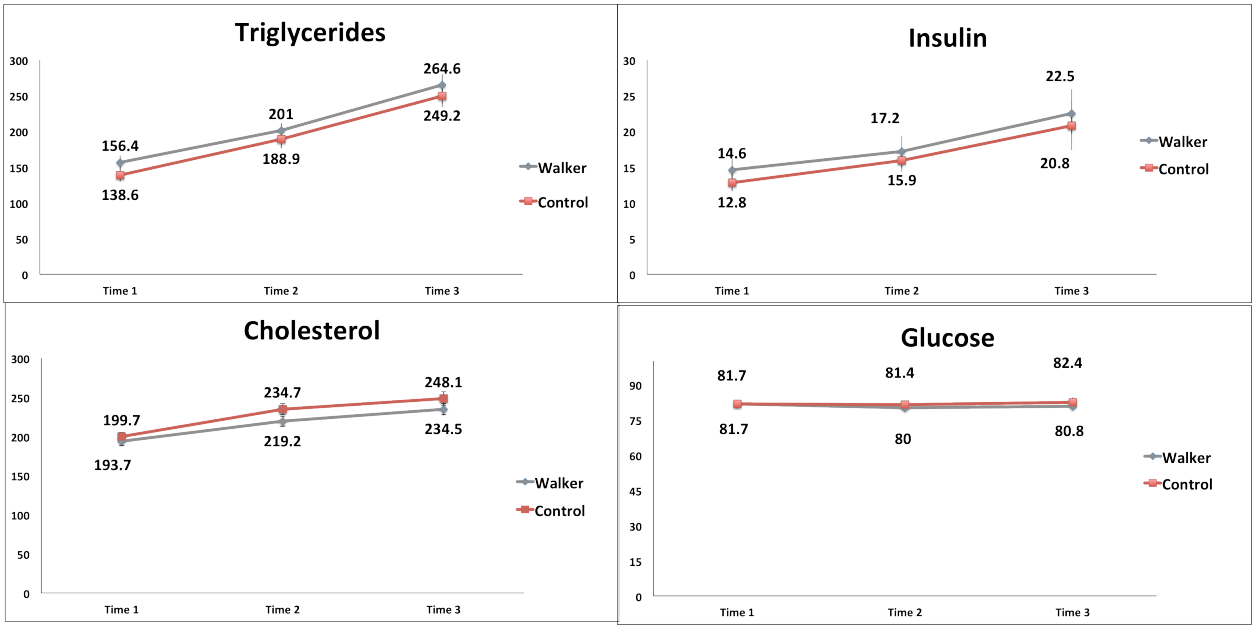

Figure 1. This figure is a line graph of means ± standard errors for triglyceride, total cholesterol, insulin, and glucose levels at times 1, 2, and 3 for the walking and the control group. Standard error bars were calculated for each time and are present on each graph. There were no significant differences noted between the control and walking groups at any time point for these variables.

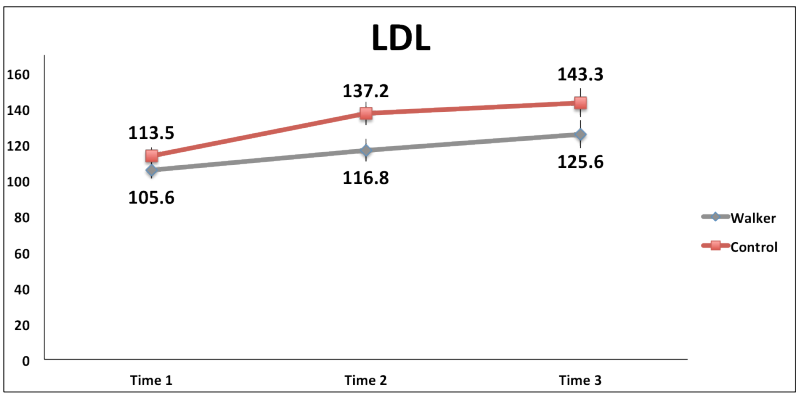

Figure 2. This figure is a line graph depicting mean ± standard error for LDL cholesterol at times 1, 2, and 3 for the walking and control group. A t-test was used to assess for differences between the groups at each time point. At time 2, which corresponds with the second trimester of pregnancy, LDL cholesterol was significantly lower for the walking group (p=0.03)

Discussion

This study compared the lipid metabolism of pregnant participants who were randomized into an exercise intervention group and control group at three points throughout their pregnancy. The data was collected and analyzed to determine whether exercise significantly affected the lipid levels of the intervention group compared to that of the control group at time 1, 2, or 3.

Our hypothesis was that exercise would exert a positive effect on lipid metabolism such that the exercise intervention group would have decreased cholesterol, triglycerides, LDL cholesterol, glucose and insulin and have increased HDL cholesterol as compared to the control group. The findings showed that there was no significant difference between groups for triglyceride, cholesterol, HDL cholesterol, insulin, or glucose levels at any point of assessment. While there were no significant differences noted between the two groups, the lipid profiles followed the physiologic changes expected in pregnancy. Triglyceride and cholesterol levels increased at the expected physiologic pattern observed in pregnancy. This pattern of increases in energy storage is necessary to ensure adequate nutrients are available to the developing fetus.

Insulin resistance also increases during normal pregnancy; therefore more insulin production is necessary to maintain the steady state of glucose that is desired in pregnancy. This was found within the study and is demonstrated on the graph in Figure 1.

There was a significant difference in LDL levels noted between the two groups at time 2 with the exercise intervention group having a lower LDL cholesterol mean compared to the control group. This demonstrates that exercise may significantly decrease LDL, "bad cholesterol", in pregnancy in response to increased activity. Because high LDL levels are associated with the endothelial dysfunction and dyslipidemia present in both cardiovascular disease and preeclampsia, decreasing this level may help to prevent these abnormal changes and in turn help to prevent preeclampsia. In order to determine the full effect of exercise on LDL levels, further analysis is necessary to determine the participant's adherence to the physical activity required in the study, as this adherence is crucial to the study's results. Future analysis should also be done to determine the effect of the woman's baseline body mass index (BMI) on lipid metabolism and the effect of studying only women with a history of preeclampsia. These three factors may have influenced the results, and it is important to determine whether exercise truly had the impact on the LDL level that was found in this analysis.

While this study provided important data on exercise's effect on lipid metabolism, it has some limitations that need to be considered. Because this study analyzed the data collected in the original study, "Exercise Intervention to Reduce Recurrent Preeclampsia", its original design and method affected the results of this analysis. One of the greatest limitations of the original study was the sample size. The intended sample size was 160 women per group; however due to the difficulty recruiting such a specific high-risk population, the study began with 123 women in total. The next issue came with keeping all participants in the study. Because all of the

participants had a history of preeclampsia, their current pregnancy was considered high-risk. As a result, primary-care providers were very cautious, and at the first sign of a potential complication, women were told they should stop exercising, and they dropped out of the study. This limitation may have been preventable had there been better communication, especially regarding common discomforts between the research team and primary care provider. If the research team had fully explained the study and potential benefits of exercise to the physician or made a joint determination as to whether the complaint of the participant was likely related to increased physical activity, they may have promoted exercise further into the pregnancy rather than being so quick to remove the woman from the study. These two factors explain the high-rate of dropouts and small sample size that limited the results of the study.

In conclusion, this analysis demonstrated the effects of moderate exercise on a woman's lipid metabolism throughout pregnancy. While there are significant metabolic changes that occur throughout a normal pregnancy to ensure adequate oxygenation and nutrition to the developing fetus, it is important to control these changes to prevent significant dyslipidemia and endothelial dysfunction. This study showed that while not all lipid levels are significantly decreased by exercise, LDL levels, a major factor in promoting endothelial dysfunction, are significantly reduced, suggesting the importance of exercise in the prevention of cardiovascular disease and preeclampsia. Further analysis is necessary to further explore the relationship between LDL metabolism and exercise as well as make up for the high drop-out rates and small sample size that prevented this study from demonstrated the full effect of exercise on lipid metabolism to be seen.

Implications for Nursing

The findings of this study encourage additional analyses to be conducted to fully understand the potential contributing factors to the reduced LDL levels reported in this study. If these study findings were replicated, or if a modified design and methods would demonstrate similar findings, then nurses, as professionals in health promotion and disease prevention, could use these findings to emphasize the importance of a woman's choices on their health and future wellbeing.

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